POST-AUTHORISATION SAFETY STUDY (PASS)
Final Study Report

Title	A post-authorisation safety study (PASS) to evaluate the long-term cardiovascular and psychiatric safety profile of methylphenidate in adult patients with attention deficit/hyperactivity disorder (ADHD) in European Countries
Version	2.0
Date of last version of the final study report	18 June 2025
EU PAS register number	EUPAS39745
Active substance	Methylphenidate hydrochloride (MPH) - ATC WHO code: N06BA04
Medicinal product	Methylphenidate hydrochloride
Product reference	N/A
Procedure number	DE/H/0690/004-010/II/043/G
Marketing authorisation holder	Medice Arzneimittel Pütter GmbH Co. KG
Joint PASS	No
Research question and objectives	The overall aim of the Post-Authorisation Safety Study (PASS) is to compare the risk of first-time cardiovascular or psychiatric events in association with new use of MPH monotherapy versus new use of non-MPH ADHD medications (lisdexamfetamine, dexamfetamine and atomoxetine; monotherapy) and versus no use of ADHD medication in adult patients aged ≥18 years newly diagnosed with ADHD, in healthcare databases of 3 European countries (Denmark, Norway, and Sweden). Primary objective 1. To compare the incidence rate of first-time cardiovascular events (composite of: hospitalisation for myocardial infarction (MIH), cardiomyopathy (CM), left-ventricular hypertrophy, hospitalisation for stroke (STR), ventricular arrhythmia (VA), sudden cardiac death or all other causes of cardiovascular death of interest) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH

	versus cumulative person-time newly treated with non-MPH ADHD medication. Secondary objectives 2. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 3. To compare the incidence rate of first-time psychiatric events of interest (composite of psychotic or manic symptoms [MANI], suicidal ideation or behaviour, aggressive and hostile behaviour, anxiety or agitation or tension, depressive symptoms [DEPR], motor or verbal tics [MOTO]) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 4. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 5. To quantify the crude cumulative incidence, describe the time to onset and define the high-risk periods and selected risk factors for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 6. To quantify the crude cumulative incidence, describe the time to onset and define the high-risk periods and selected risk factors for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. Exploratory objectives 7. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication, by calendar time prior to and post introduction of extended-release MPH formulations. 8. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative

	person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication, by cumulative dose. 9. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication, by sex and age. 10. To compare, separately, the incidence rate of MIH, CM, left-ventricular hypertrophy, hospitalisation for STR, VA, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 11. To compare, separately, the incidence rate of all-cause death (DIED), and incidence rate of hypertension (HYPE), cardiac valve disease (CARD) and pulmonary hypertension (PHYP) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 12. To compare, separately, the incidence rate of first-time psychiatric events of interest (MANI; suicidal ideation or behaviour; aggressive and hostile behaviour; anxiety, agitation or tension [ANXI]; DEPR; MOTO) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. If a significant increase in the incidence rate of the cardiovascular composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 2) when pooled across all countries, the following additional objectives would be assessed: 13. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication, by calendar time prior to and post introduction of extended-release MPH formulations. 14. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication, by cumulative dose. 15. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication, by sex and age.

	16. To compare, separately, the incidence rate of MIH, CM, left-ventricular hypertrophy, hospitalisation for STR, VA, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 17. To compare, separately, the incidence rate of DIED, and incidence rate of HYPE, CARD and PHYP in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. If a significant increase in the incidence rate of the psychiatric composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 4) when pooled across all countries, the following additional objective would be assessed: 18. To compare, separately, the incidence rate of first-time psychiatric events of interest (MANI; suicidal ideation or behaviour; aggressive and hostile behaviour; ANXI; DEPR; MOTO) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. The above objectives were completed over a five-year follow-up period. If a sufficient number of patients are still available after 5 years (≥30% of cohort) until 10 years (≥10% of cohort), the following additional objectives would be assessed using a ten-year follow-up period: 19. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 20. To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 21. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 22. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 23. To quantify the crude cumulative incidence, describe the time to onset for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly

	exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 24. To quantify the crude cumulative incidence, describe the time to onset for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.
Countries of study	Denmark, Norway, Sweden
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This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – post-authorisation safety studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

1. ABSTRACT

Title	A post-authorisation safety study (PASS) to evaluate the long-term cardiovascular and psychiatric safety profile of methylphenidate in adult patients with attention deficit/hyperactivity disorder (ADHD) in European Countries
Keywords	Post-Authorisation Safety Study, ADHD, methylphenidate, cardiovascular events, psychiatric events
Rationale and background	Medikinet® retard, a methylphenidate (MPH) containing product marketed by Medice, is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over and adults when remedial measures alone prove insufficient. Other ADHD treatments include dexamfetamine, lisdexamfetamine, and atomoxetine, which composed the non-MPH group in this study. The short- and long-term efficacy of MPH is well-established. Long-term safety data on cardiovascular (CV) risks in adults treated with MPH showed minor mean pre-post elevations in blood pressure (BP) and pulse rate (PR), yet without an increase in serious cardiac outcomes. However, case reports of sudden death (SUD), stroke (STR), and myocardial infarction (MI) reported for adult patients treated with psychostimulants have led to regulatory concerns on the long-term benefit-risk balance and requests for studies to assess these outcomes. MPH use is also associated with psychiatric effects, insomnia, decreased appetite, headache, and anorexia. These adverse CV and psychiatric events have however been observed mainly in clinical trials. There is limited and inconsistent data from pharmacoepidemiologic studies on MPH use and adverse CV or psychiatric events, especially among adults.
Research question and objectives	The overall aim of the Post-Authorisation Safety Study (PASS) is to compare the risk of first-time CV or psychiatric events in association with new use of MPH monotherapy versus new use of non-MPH ADHD medications (lisdexamfetamine, dexamfetamine and atomoxetine; monotherapy) and versus no use of ADHD medication in adult patients aged ≥18 years newly diagnosed with ADHD, in healthcare databases of 3 European countries. Primary objective 1. To compare the incidence rate of first-time CV events composite of: hospitalisation for myocardial infarction (MIH), CM, left-ventricular hypertrophy (LVH), hospitalisation for STR, ventricular arrhythmia (VA), sudden cardiac death or all other causes of CV death of interest; termed as major cardiovascular adverse

	events [MACE]) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. Secondary objectives 2. To compare the incidence rate of first-time CV events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 3. To compare the incidence rate of first-time psychiatric events of interest (composite of: psychotic or manic symptoms [MANI], suicidal ideation or behaviour (SUIC), aggressive and hostile behaviour [AGGR], anxiety or agitation or tension [ANXI], DEPR, MOTO) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 4. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 5. To quantify the crude cumulative incidence, describe the time to onset and define the high-risk periods and selected risk factors for CV events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 6. To quantify the crude cumulative incidence, describe the time to onset and define the high-risk periods and selected risk factors for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. Exploratory objectives 7. To compare the incidence rate of first-time CV events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD

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	MPH versus cumulative person-time not receiving ADHD medication, by cumulative dose. 15. To compare the incidence rate of first-time CV events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication, by sex and age. 16. To compare, separately, the incidence rate of MIH, CM, LVH, hospitalisation for STR, VA, sudden cardiac death, or all other causes of CV death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 17. To compare, separately, the incidence rate of DIED, and incidence rate of HYPE, CARD and PHYP in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. If a significant increase in the incidence rate of the psychiatric composite (PSYC) endpoint was observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 4) when pooled across all countries, the following additional objective would be assessed: 18. To compare, separately, the incidence rate of first-time psychiatric events of interest (MANI; SUIC; AGGR; ANXI; DEPR; MOTO) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. The above objectives were completed over a 5-year follow-up period. If a sufficient number of patients were still available after 5 years (≥30% of cohort) until 10 years (≥10% of cohort), the following additional objectives would be assessed using a 10-year follow-up period: 19. To compare the incidence rate of first-time CV events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 20. To compare the incidence rate of first-time CV events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.

	21. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 22. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 23. To quantify the crude cumulative incidence, describe the time to onset for CV events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 24. To quantify the crude cumulative incidence, describe the time to onset for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.
Study design	This was a retrospective observational cohort study conducted in 3 European countries (Denmark, Norway, and Sweden) using secondary data. A new user design was applied. The study population were comprised of a cohort of adults newly diagnosed with ADHD, on or after the age of 18 years. Cohorts were constructed for each of the 2 grouped adverse effects (CV disorders or psychiatric disorders). Comparisons were made according to contributed treatment episodes of person-time of new use of MPH, episodes of new use of non-MPH or episodes of no treatment: (i) Patient contributed person-time during first episode of new use of MPH (MPH person-time). (ii) Patient contributed person-time during first episode of new use of other treatments for ADHD (dexamfetamine, lisdexamfetamine, atomoxetine) (non-MPH person-time). (iii) Patient contributed person-time of no use of any ADHD medication post diagnosis (untreated person-time).

	Patients were followed from the index date (ADHD diagnosis date) to assess the occurrence of CV or psychiatric events of interest, as appropriate.
Setting	The study period of started from 13 June 2008 for Sweden, 06 May 2011 for Norway, and from 29 September 2006 for Denmark through to 31 December 2019, in order to allow for the minimum lookback period for confounders before the enrolment (12 months) and to start the study not prior to the availability of prescription data for MPH and at least one active comparator in the selected European Union (EU) market(s). In each country, patients who were aged 18 years or more and had a diagnosis of ADHD were identified as eligible for inclusion into the study using the National Patient Register. Individual patient data were thereafter linked to the National Dispensed Drug Register and the Cause of Death Register. The following selection criteria were applied for the data extraction: Inclusion criteria for data extraction: • A diagnosis recorded at any time in the data source of ADHD based on International Statistical Classification of Diseases, 10th Revision (ICD-10) codes F90 (Hyperkinetic disorders) or F98.8 (Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence). • Age 18 years or more at ADHD diagnosis. • Continuous enrolment in the database for >12 months prior to date of first diagnosis. • No dispensed prescription for ADHD medication in the prior 12 months before cohort entry (defined as the index diagnosis of ADHD). Exclusion criteria for data extraction: • Patients with missing age or sex. • ADHD diagnosis prior to and including age 17 years. These patients by definition cannot be considered as adults newly diagnosed with ADHD in this study and are instead prevalent cases of the indication for treatment. To address the research questions related to the primary and secondary endpoints separate cohorts were created, and cohort-specific selection criteria, nested within the criteria for data extraction, were applied. These cohorts were referred as the CV and psychiatric cohorts, respectively.

Subjects and study size	For the sample size calculation, it was assumed an effect size of 1.8 being observed at the end of 5-years follow-up, where the incidence in the reference group would be 3/1000, with 80% power and 5% significance. Additionally, 85% attrition was assumed over 5 years follow-up. Therefore, a minimum of 11,997 person-years for the MPH exposed person-time, non-MPH exposed person-time and untreated person-time were needed. Accordingly, at least 6,574 patients must be identified in each exposure group assuming a ratio of 1:1:1.
Variables and data sources	**ADHD prescription data were used to defined exposure.** **Primary endpoint** The primary endpoint for the CV cohort was a composite of the following CV events of interest: • MIH • Hospitalisation for STR • VA • CM • LVH • SUD • All causes of cardiovascular death (CVDIED) **Secondary endpoints** The secondary endpoints included the following: **Psychiatric events** The endpoint for analysis of the psychiatric cohort was a composite of the following psychiatric events of interest: • MANI • SUIC • AGGR • ANXI • DEPR • MOTO **CV events** Secondary endpoints for the CV cohort also included the components of the primary composite CV endpoint as individual endpoints: • MIH • Hospitalisation for STR • VA • CM • LVH • SUD

	• CVDIED as well as following additional CV endpoints: • DIED • HYPE • CARD • PHYP Exploratory endpoints for the psychiatric cohort also included the components of the primary composite psychiatric endpoint (PSYC) as individual endpoints: • MANI • SUIC • AGGR • ANXI • DEPR • MOTO **Covariates** included age, sex, calendar year of diagnosis, season of diagnosis, use of psychotropic and other selected drugs, CV risk factors, and psychiatric risk factors. **Data Sources:** • The National registries from Denmark, Norway, and Sweden
Results	In this cohort study, newly diagnosed adult ADHD patients in Denmark, Norway, and Sweden were included from national registers. The first treatment episode of MPH or non-MPH exposure and unexposed period since diagnosis date were studied. Separate sub-cohorts for CV and psychiatric outcomes were established. MPH was the largest exposure group in all 3 countries, followed by unexposed group, while non-MPH group was the smallest. In Denmark, the composite cardiovascular event (MACE+) sub-cohort included 11,963 patients with a first treatment episode of MPH, 3,738 patients with a first treatment episode of non-MPH medications, and 5,053 untreated patients. In Norway, there were 16,945 patients with a first treatment episode of MPH, 1,700 with non-MPH medications, and 9,208 untreated patients. In Sweden, the sub-cohort included 50,105 patients with a first treatment episode of MPH, 11,144 with non-MPH medications, and 21,594 untreated patients. These patients were followed for up to 5 years, but the median (first quartile [Q1] to third quartile [Q3]) length of the first treatment episode from treatment onset to end of follow-up was 7.30 (3.27 to 20.07), 8.67 (3.57 to 20.80), and 6.70 (2.89 to 17.45) months in the MPH treated group in Denmark, Norway, and Sweden, respectively, and 5.60 (2.73 to 13.73), 4.80 (2.53 to 11.03), and 4.27 (2.40 to 10.15) months in the non-MPH group for the MACE+ sub-cohort. In the MPH treated group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 28.83, 31.98, and 31.70 years; and 46.70%, 50.56%, and 50.59% were female. Risk factors for CV conditions were infrequent in general, while history of psychotropic drug use was the most frequent characteristic and reported in 38.45%, 31.82%, and 48.11% of the MPH treated

	patients, respectively, in the 3 countries. In the non-MPH treated group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 28.96, 33.34, and 32.42 years; and 38.01%, 33.18%, and 46.73% were female. History of psychotropic drug use was reported in 45.02%, 40.71%, and 51.14% of the non-MPH treated patients. In the unexposed group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 29.12, 32.58, and 32.12 years; and 42.07%, 42.94%, and 47.39% were female. History of psychotropic drug use was the most frequent characteristic observed in 31.15%, 30.38%, and 43.72% of the unexposed patients. Crude incidence rates of MACE+, per 1,000 person-years, during 0–5-year follow-up interval, respectively, in Denmark, Norway, and Sweden were 2.49 (95% confidence interval [CI]: 1.75-3.43), 2.35 (95% CI: 1.74-3.09), and 1.98 (95% CI: 1.63-2.38) in the MPH group; 4.17 (95% CI: 2.34-6.88), 5.24 (95% CI: 2.11-10.81), and 2.96 (95% CI: 1.88-4.45) in the non-MPH group; and 2.58 (95% CI: 1.98-3.30), 2.54 (95% CI: 2.05-3.10), 2.39 (95% CI: 2.09-2.73) in the unexposed group. In Denmark, the PSYC sub-cohort included 6,518 patients with a first treatment episode of MPH, 1,979 patients with a first treatment episode of non-MPH medications, and 2,891 untreated patients. In Norway, there were 9,844 patients with a first treatment episode of MPH, 855 with non-MPH medications, and 5,880 untreated patients. In Sweden, the sub-cohort included 20,077 patients with a first treatment episode of MPH, 3,806 with non-MPH medications, and 8,957 untreated patients. Similar to the MACE+ sub-cohort, the length of the first treatment episode from treatment onset to end of follow-up was on average 14.77, 15.02, and 12.62 months in the MPH treated group in Denmark, Norway, and Sweden, respectively, and 11.31, 9.43, and 7.99 months in the non-MPH group for the PSYC sub-cohort. In the MPH treated group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 28.46, 31.44, and 31.46 years; and 38.86%, 46.17%, and 41.58% were female; and history of psychotropic drug use was reported in 22.98%, 21.41%, and 26.55% of the patients. In the non-MPH treated group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 28.74, 33.19, and 32.46 years; and 30.47%, 28.65%, and 61.80% were female; and history of psychotropic drug use was reported in 26.07%, 28.54%, and 29.14% of the patients. In the unexposed group, respectively in Denmark, Norway, and Sweden, the mean age at diagnosis date was 28.96, 31.91, and 31.25 years; and 37.18%, 38.84%, and 38.82% were female; and history of psychotropic drug use was the most frequent characteristic 18.23%, 21.99%, and 23.87% of the patients. Crude incidence rates of PSYC, per 1,000 person-years, during the 0–5-year follow-up interval, respectively, in Denmark, Norway, and Sweden were 41.46 (95% CI: 37.10-46.20), 49.12 (95% CI: 45.26-53.22), and 91.41 (95% CI: 87.37-95.58) in the MPH group; 42.93 (95% CI: 33.98-53.50), 72.42 (95% CI: 53.40-96.02), and 92.25 (95% CI: 80.81-104.86) in the non-MPH group; and 66.39 (95% CI: 61.58-71.48), 81.82 (95% CI: 77.82-85.97), and 83.27 (95% CI: 80.04-86.59) in the unexposed group.

	For both MACE+ and PSYC, no high-risk periods, ie, periods with significantly higher incidence than the first 3 months after MPH or non-MPH onset, were identified. In the unexposed group, the incidence of MACE+ was similar in the first 3 months after diagnosis and all following 3-month intervals in all countries; and the incidence of PSYC was significantly higher in the first 3 months after the diagnosis date than later intervals. For the primary objective, non-significantly decreased risk of MACE+ was observed comparing cumulative exposure to MPH with non-MPH. The adjusted hazard ratios (HRs) in Denmark, Norway, and Sweden were 0.82 (95% CI: 0.68-1.19), 0.97 (95% CI: 0.72-2.51), and 0.78 (95% CI: 0.66-1.00) for 1-year cumulative exposure, respectively; 0.56 (95% CI: 0.31-1.70), 0.90 (95% CI: 0.38-15.73), and 0.48 (95% CI: 0.29-1.01) for 3-year cumulative exposure; and 0.38 (95% CI: 0.15-2.42), 0.84 (95% CI: 0.20-98.73), and 0.30 (95% CI: 0.13-1.01) for 5-year cumulative exposure. The pooled HR of 5-year cumulative exposure was 0.45 (95% CI: 0.03-6.30). For the secondary objectives, decreased risk for MACE+ was observed comparing MPH with the unexposed group. The adjusted HRs in Denmark, Norway, and Sweden were, respectively, 0.96 (95% CI: 0.91-1.00), 0.94 (95% CI: 0.90-0.99), and 0.96 (95% CI: 0.88-1.04) for 1-year cumulative exposure, respectively; 0.88 (95% CI: 0.77-0.99), 0.82 (95% CI: 0.74-0.98), and 0.88 (95% CI: 0.67-1.11) for 3-year cumulative exposure; and 0.80 (95% CI: 0.64-0.98), 0.72 (95% CI: 0.61-0.97), and 0.81 (95% CI: 0.52-1.20) for 5-year cumulative exposure. The pooled HR of 5-year cumulative exposure was 0.78 (95% CI: 0.06-9.41). For the PSYC sub-cohort, inconsistent risk estimates were observed in the 3 countries. The adjusted HRs for PSYC comparing the MPH group with the non-MPH group, respectively, in Denmark, Norway, and Sweden were 1.21 (95% CI: 1.07-1.46), 1.10 (95% CI: 0.94-1.44), and 0.98 (95% CI: 0.89-1.10) for 1-year cumulative exposure; 1.79 (95% CI: 1.22-3.10), 1.33 (95% CI: 0.82-2.96), and 0.95 (95% CI: 0.70-1.35) for 3-year cumulative exposure; and 2.64 (95% CI: 1.40-6.57), 1.61 (95% CI: 0.72-6.11), and 0.92 (95% CI: 0.55-1.64) for 5-year cumulative exposure. The pooled HR of 5-year cumulative exposure was 1.57 (95% CI: 0.13-19.52). The adjusted HRs for PSYC comparing MPH with the unexposed group, respectively, in Denmark, Norway, and Sweden were 0.97 (95% CI: 0.95-0.99), 0.97 (95% CI: 0.96-0.97), and 1.08 (95% CI: 1.05-1.12) for 1-year cumulative exposure; 0.93 (95% CI: 0.87-0.98), 0.90 (95% CI: 0.87-0.93), and 1.28 (95% CI: 1.16-1.39) for 3-year cumulative exposure; and 0.88 (95% CI: 0.79-0.96), 0.84 (95% CI: 0.80-0.88), and 1.50 (95% CI: 1.29-1.73) for 5-year cumulative exposure. The pooled HR of 5-year cumulative exposure was 1.03 (95% CI: 0.09-12.46). Exploratory analyses of separate CV outcomes were conducted only in Sweden. Increased risks of MIH and CVDIED in Sweden comparing the MPH with non-MPH group, and the HRs of MIH were 1.51 (95% CI: 1.14-5.05), 3.45 (1.49-128.58), and 7.89 (95% CI: 1.95-3,275.74), respectively, for 1-, 3-, and 5-year

	cumulative exposure. The HRs of CVDIED were 1.91 (95% CI: 1.38-6.60), 7.02 (95% 2.64-287.35), and 25.75 (95% CI: 5.04-12,512.43), respectively, for 1-, 3-, and 5-year cumulative exposure. For exploratory analyses of separate psychiatric outcomes, inconsistent results were observed in the 3 countries. Increased risks were observed for MANI, ANXI, and AGGR in Denmark; AGGR in Norway; and MANI and SUIC in Sweden comparing the MPH with non-MPH group. The significantly increased HRs for 1-, 3-, and 5-year exposure, respectively, were 1.21 (95% CI: 1.01-1.76), 1.77 (95% CI: 1.04-5.48), and 2.59 (95% CI: 1.06-17.03) for MANI in Denmark; 1.32 (95% CI: 1.10-1.81), 2.29 (95% CI: 1.32-5.95), and 3.99 (95% CI: 1.60-19.52) for ANXI in Denmark; 1.28 (95% CI: 1.06-2.02), 2.09 (95% CI: 1.18-8.20), and 3.43 (95% CI: 1.32-33.34) for AGGR in Denmark; 1.34 (95% CI: 1.02-4.50), 2.39 (95% CI: 1.05-91.38), and 4.27 (95% CI: 1.08-1,853.81) for AGGR in Norway; 1.26 (95% CI: 1.01-1.55), 2.01 (95% CI: 1.04-3.75), and 3.21 (95% CI: 1.06-9.06) for MANI in Sweden; 1.83 (95% CI: 1.18-3.57), 6.10 (95% CI: 1.64-45.69), and 20.39 (95% CI: 2.27-583.84) for SUIC in Sweden.
Discussion	In this large cohort study based on national registers in Denmark, Norway, and Sweden, adults with newly diagnosed ADHD were followed for up to 5 years to address the CV safety of long-term MPH exposure. As secondary objectives, the risks for separate CV outcomes and composite as well as separate PSYC outcomes were additionally evaluated. Overall, there was no increased risk of major CV adverse events in adult patients with ADHD when comparing those newly exposed to MPH with those newly exposed to non-MPH medications or unexposed. Consistent results were observed across all 3 study countries, contradicting the assumption that MPH increases the overall CV risk. However, as part of the secondary objectives, and in accordance with the CV risk precautions outlined in the Summary of Product Characteristics (SmPC), potential risks for MI and cardiac death were noted. These findings were based on a small number of events and should be interpreted cautiously. The psychiatric safety of MPH was additionally evaluated as part of secondary objectives. No increased risk of psychiatric outcomes was observed when comparing patients newly exposed to MPH with non-MPH medications in Sweden, which is the country with the most comprehensive psychiatric data collection within the 3 study countries, while non-significantly increased risk in Norway and significantly increased risk in Denmark were reported. Increased risk of psychiatric outcomes was observed in the MPH group compared with unexposed group in Sweden, but not in Denmark and Norway. The observed contradictory results are likely due to limitations related to the complexity and overlap of ADHD diagnosis and other psychiatric conditions, lines of treatment, and the use of secondary data that cover specific care settings to capture the occurrence of psychiatric conditions. The study findings suggest that MPH has a comparable long-term CV and psychiatric safety profile to non-MPH treatments in adult patients with ADHD living in Denmark, Norway, and Sweden. Overall, the findings of this study align with the established benefit-risk profile of MPH in adult patients. The CV and

	psychiatric risks investigated in this study are already comprehensively emphasised in the current SmPC of MPH-containing products, particularly within the sections on contraindications, warnings, and precautions.
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